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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/491,549	01/26/00	BAULCOMBE D	

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1601 MARKET STREET
PHILADELPHIA PA 19103-2307

EXAMINER	
PARAS JR,P	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 06/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/491,549	BAULCOMBE ET AL.	
	Examiner	Art Unit	
	Peter Paras	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-17,21,26-29 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-17,21,26-29 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Applicant's amendment filed on April 27, 2001 (Paper No. 12) has been entered. Claims 1, 8-11, 14, 17, 21, and 26 have been amended. Claims 2, 3-4, 18-20, 22-25, and 30-31 have been cancelled. New claims 33-34 have been added. Claims 1, 5-17, 21, 26-29, and 32-34 are pending and are currently under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 10/27/99. It is noted, however, that applicant has not filed a certified copy of the British application as required by 35 U.S.C. 119(b).

The following are new grounds of rejection under 35 USC 112, 2nd paragraph:

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-11, 21, and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 as written is indefinite. Claim 1 is directed to methods of determining the occurrence of target gene silencing by detecting the presence of small RNA molecules. Claim 1, as written, recites the step of analyzing a plant nucleic acid extract for the presence of SRMs. Claim 1, however, as written does not describe the process for

analyzing the nucleic acid extract for the presence of SRMs. The specification has taught that Northern blot analysis can be used to identify SRMs. Additionally, the claims do not correlate the presence of SRMs with any particular phenotype in a plant to demonstrate silencing of a particular gene. It is unclear how only the presence of SRMs can demonstrate the occurrence of gene silencing.

It is maintained that the claims have not been amended to read on the elected species –plant as noted in Paper No. 10, on page 5, at the top.

The following are new grounds of rejection under 35 USC 102:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5-10, 12-17, 21, 26-29, and 32-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamilton et al (Science, 1999, 286: 950-952).

Hamilton et al teach methods of identifying small RNA molecules (SRMs) that are 25 nucleotides in length that may be responsible for gene silencing. Hamilton et al teach that the SRMs, which can be sense or antisense, are identified by Northern blotting. See figures 1-3. Hamilton et al teach that the SRMs are associated with target genes by sequence analysis. Hamilton et al also teach that the target genes may be

associated with pathogen resistance or ripening. Hamilton et al teach transgenic tomatoes comprising an ACO-oxidase transgene operably linked to the 35S promoter. The transgene when expressed produce mRNA molecules that silence the endogenous ACO gene. See page 950.

Thus, the teachings of Hamilton et al clearly anticipate all of the instant claim limitations.

Claims 1, 5-10, 12-17, 21, 26-29, and 32-34 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by meeting presentation at Leysin, Switzerland, February 25-28, 1999 (IDS, C6).

Balcoumbe et al teach methods of identifying small RNA molecules (SRMs) that are 25 nucleotides in length that may be responsible for gene silencing. Balcoumbe et al teach that the SRMs, which can be sense or antisense, are identified by Northern blotting. Balcoumbe et al teach that the SRMs are associated with target genes by sequence analysis. Balcoumbe et al also teach that the target genes may be associated with pathogen resistance or ripening. Balcoumbe et al teach transgenic tomatoes comprising an ACC-oxidase transgene operably linked to the 35S promoter. The transgenes when expressed produce mRNA molecules that silence the endogenous ACO gene. Thus, all of the instant claim limitations are anticipated.

Claims 1, 5-10, 12-17, 21, 26-29, and 32-34 rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hamilton et al (poster presentation, July 25-30, 1999, IDS-C7).

Hamilton et al teach methods of identifying small RNA molecules (SRMs) that are 25 nucleotides in length that may be responsible for gene silencing. Hamilton et al teach that the SRMs, which can be sense or antisense, are identified by Northern blotting. Hamilton et al teach that the SRMs are associated with target genes by sequence analysis. Hamilton et al also teach that the target genes may be associated with pathogen resistance or ripening. Hamilton et al teach transgenic tomatoes comprising an ACO-oxidase transgene operably linked to the 35S promoter. The transgene when expressed produce mRNA molecules that silence the endogenous ACO gene.

The following are new grounds of rejection under 35 USC 103 necessitated by Applicant's amendment to the claims which now include the limitation of small RNA molecules that are 21-25 nucleotides in length:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

Claims 1, 5-17, 21, 26-29, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waterhouse et al (PNAS, 1998, 95: 13959-13964) and Wassenegger (Plant Mol. Biol., 1998, 349-362) taken with Dougherty (Cur. Opin. Cell Biol., 1995, IDS).

Waterhouse et al teach post-transcriptional gene silencing (PTGS) in transgenic tobacco comprising nucleotide sequences that produce antisense RNA molecules which form double stranded mRNA with RNA transcripts of the potato virus Y (PVY). Waterhouse et al specifically disclose the constructs which produce the antisense RNA molecules the silence the Pro gene of PVY. See page 13960. Waterhouse et al identify RNA molecules that silence the Pro gene of PVY by Northern blot analysis. See figures 3 and 5, and also Materials and Methods section for Northern blot and RNA isolation procedures. In addition, Wassenegger teaches that post-transcriptional gene silencing occurs by the formation of double-stranded RNA molecules between a target sequence and a small RNA molecule. Particularly, Wassenegger et al teach that a 43 nucleotide long element was highly complementary to a part of the coding region of the chalcone synthase gene in the petunia, wherein base pairing of the complementary regions forms double-stranded RNA molecules which are degraded. See page 351, column 1, paragraph 1. Wassenegger et al also suggest that homology of 60 to 130 bp or 10-100 bp between an inactivating transgene and the target sequence can lead to PTGS. See page 356.

The collective teachings of Waterhouse et al and Dougherty et al differ from the claimed invention by not teaching methods of determining the occurrence of gene silencing by detecting small RNA molecules that are 21-25 nucleotides in length.

However at the time the claimed invention was made, Dougherty et al teaches that sense or antisense RNA molecules hybridize with target mRNA to form an inactive double-stranded RNA intermediate that is rapidly eliminated from the cell. Doughtery et al teaches that short oligonucleotides (10-40 nucleotides) can produce antisense RNA molecules that hybridize with a target RNA molecule to form double stranded RNA molecules. See pages 399-400. Doughtery et al further report that in *C. elegans* two transcripts of the lin-14 gene (21nt and 69 nt) are complementary to a lin-4 gene mRNA transcript; it is suggested that the 21 and 69 nt transcripts bind to the lin-4 transcript and decrease its translation. See page 400, column 1. Doughtery et al suggest that gene suppression by sense and antisense transcripts are mediated by the same process in eukaryotic cells. See page 401 and figures 1-2. Doughtery further suggest that the mechanism of gene suppression in eukaryotes is sequence-driven by small RNA molecules that may be approximately 20 nt which bind to a target mRNA molecule and effectively suppress expression. See figure 1. Doughtery also teaches that plants contain an RNA-dependent RNA polymerase activity that can randomly copy any RNA molecule and make small (10-75 nucleotide) complementary RNAs (cRNAs). Such small RNA molecules would be key in binding to a target and determining which RNA is eliminated. It is suggested that cRNAs operate in a cis and trans fashion and that the entire target RNA is a substrate. See page 402.

Accordingly, in view of the teachings of Doughtery et al, it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to modify the collective teachings of Waterhouse et al and Wassenegger et al by identifying small RNA molecules that are approximately 10-75 nucleotides in length by Northern blot analysis with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to identify such small RNA molecules as both Wassenegger et al and Dougherty et al have suggested that such small RNA molecules are responsible for PTGS. Furthermore, one of ordinary skill would have been sufficiently motivated to identify such small RNA molecules as it was an art-recognized goal to elucidate the mechanism of PTGS as taught by both Waterhouse et al (page 13964 final two paragraphs) and Wassenegger et al (page 356).

Thus, the claimed invention, as a whole is prima facie obvious in the absence of any evidence to the contrary.

Applicant's arguments have been considered but are not found persuasive. Applicants have argued that there is no motivation to combine the cited references, Waterhouse et al and Wassenegger et al. Particularly, Applicants have argued that neither Waterhouse et al nor Wassenegger et al has taught small RNA molecules of about 25 nucleotides in length. Applicants have also argued that neither reference teaches the mechanism of PTGS. See pages 6-13 of the amendment.

In response, it is initially noted that Applicant's amendment to the claims necessitated the new grounds of rejection set forth above. The claims are for the most part directed to identifying small RNA molecules. Claims 1-2, 5-11, 21, and 32-34

required that the RNA molecules be 21-25 nucleotides in length. Claims 12-17, 26-29, and 32 do not require an RNA molecule of any particular length. The cited references suggest that RNA molecules of lengths ranging between 10-100 nucleotides may be responsible for PTGS. Particularly, Wassenegger has suggested that RNA molecules of lengths ranging from 10-100 bp may be responsible for PTGS. Also, Doughtery has suggested that RNA molecules of 10-40 nucleotides may be responsible for PTGS in eukaryotes, and specifically suggests that molecules approximately 10-20 nucleotides may be responsible for PTGS. Doughtery also has reported the observation that a 21 nucleotide RNA transcript may be responsible for gene silencing in C. elegant. Although the mechanism of PTGS may not have been elucidated by the cited references, the references clearly have provided ample motivation to identify RNA molecules ranging from 10-100 nucleotides in length that may be responsible for PTGS, clearly encompassing the recited 21-25 nucleotide length RNA molecules of the some of the instant claims. Waterhouse et al has taught Northern blot analysis as the method for identifying the small RNA molecules. The instant claims and specification do not differ in the method of identifying the small RNA molecules but rather concur that Northern blot analysis would be the method of choice. One of ordinary skill in the art understands that the parameters of polyacrylamide gels used for identifying such RNA molecules are dependent on the size of the molecules to be identified and should be modified accordingly. The combination of references (Waterhouse, Wassenegger, and Doughtery) has taught that gene silencing may occur by formation of double stranded RNA molecules between a target RNA molecule and a small RNA molecule, such as

the SRMs required by the instant claims, that Northern blot analysis can be used to identify such SRMS, and that SRMs may be between 10-40 nucleotides in length, particularly between 10-21 nucleotides in length. The combination of references has also provided ample motivation for identifying small RNA molecules that may be involved in PTGS.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

Art Unit 1632

JILL D. MARTIN
PRIMARY EXAMINER